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(57) Abstract

The process of polyphase fluid extraction of active therapeutic components from plant matter of Symphytum species is described. The preparation process for CF Symphytum Extracts includes multiple sequential stages of diffusional transfer of the active constituents into liquid and/or vapor extraction phases under contact conditions of forced convection at controlled temperature and pressure. Therapeutic formulations based on CF Symphytum Extracts including emulsions, aerosols, liposomes and controlled-release devices are presented. Treatment methods for a variety of skin conditions and complications of specific diseases are indicated.

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PREPARATION OF CONCENTRATED FLUID SYMPHYTUM EXTRACTS, THERAPEUTIC FORMS AND METHODS OF USE

BACKGROUND OF THE INVENTION

Alcohol or glycol extract solutions of *S. officinale*, which is called "Comfrey" in English, are well known as wound-healing agents as used in topical preparations.

It has long been desired to develop topical compounds with concentrated levels of healing extract that are high enough to give a distinct healing response to skin or mucous membranes while at the same time having skin moisturizing properties. The "ideal" product should have an extended shelf life e.g., 9 months to 2 years. Further, it is desirable that the product does not create a burning sensation on an open wound such as occurs with alcohol or propylene glycol preparations containing "Comfrey".

"Comfrey" has been recognized for decades for its healing properties, particularly for its ability to stimulate epithelial development externally in the case of skin damage or breakdown and internally in the case of stomach ulcers. Original applications were using a "Comfrey" tea made by boiling the leaves and stems or the roots in liquid water for a short time. The filtered liquid-solution product, tea, was taken orally for various medical symptoms or it could be applied externally to the skin surface. MacAllister (1902) reports that poultices were made by mashing or grinding fresh "Comfrey" leaves or roots and applying the resulting fibrous slurry directly to wounds to stimulate healing. Alcohol tinctures were made by using pure liquid alcohol as defined by the *U.S. Pharmacopeia* and water to extract the healing properties from "Comfrey" roots. After filtration to remove the solids, that tincture was used for external applications to promote healing. *Homeopathic Pharmacopeia* (1978) describes a typical preparation method based upon dissolved "Comfrey" extracts. No patent or research publication could be found which describes extraction of "Comfrey" by fluids other than single- phase, single- component liquids.

US3930000 teaches that solvent extracts of the roots of "Comfrey" contain a natural predecessor of synthetic allantoin which is known as 5-ureidohydantoin in the chemical literature. US4670263 discloses filtered propylene glycol compounds containing stem and leaf extracts of *Symphytum officinale*, "Comfrey", along with additives including synthetic allantoin, ascorbic acid, chlorophyll, carotene and lanolin which are claimed to be effective for treating bovine mastitis and bovine metritis. These "Comfrey propylene glycol extracts" appear to be defined by the process of soaking from 283-681 grams of "green Comfrey plant" in about 3931 grams of liquid propylene glycol; after filtration to remove suspended solid matter and the coarse fibrous material, the filtrate solution is then further diluted with about 421-3459 grams of water. Because no data are given for the weight of solids separated by the filtration step of the technique, it is impossible to calculate the actual resulting level of "Comfrey extract" dissolved and/or dispersed in either the propylene-glycol stage or the final-dilution stage. By analogy with other extracts from plant tissue, it is estimated that the active "Comfrey components" extracted by typical practice amounts to approximately 0.01 to 0.02 wt. % of the final diluted preparation. US4847084 discloses two ointments for treatment of decubitus ulcers, Decubitane #1 and #2, which are based upon a debriding enzyme, fibrinolysin, with additives including chlorophyll and povidone-iodine. US3622668 discloses a scar-inhibiting lotion for treatment of livestock

injuries which contains phenol, retinol, ergosterol and olive oil, or fish oil. None of the claimed "Comfrey" treatment formulations for humans or other mammals are emulsions, vesicles, liposomes, aerosols or micelles.

Several commercial sources offer "Comfrey -containing" topical ointments e.g., human or veterinary grades, for treatment of skin irritations, rashes and minor wounds. These consist of "Comfrey" liquid ethanol extracts mixed with an oily base. These oily bases typically contain various oils including almond and other vegetable oils blended with beeswax. Any suspensions or slurries present in these products appear to be stable against separation upon shelf storage at room temperature at least for a short time.

Commercial products that are labeled as containing "Comfrey" extract appear to have variable "Comfrey" contents below 0.01 wt. %. Generally, commercial "Comfrey"-containing products are comprised of formulas with the base having over 50 wt. % wax and oil, high levels of propylene glycol, and/ or high levels of alcohol. No evidence can be found of a true O/W emulsion with either consistent or high levels of "non-water Comfrey components" in the final formulation i.e., greater than 0.02 wt. %.

In order to evaluate the characteristics of propylene-glycol-based Symphytum extracts with 25-75 vol. % propylene glycol, experimental solution-type topical formulations were prepared and applied to various kinds of human skin injuries and diseases. Although these extracts exhibited significant healing properties on epithelial tissue, their use often produced an undesirable burning sensation on an open wound or sensitive skin areas.

One outgrowth of this experimentation was development of a preparation which consisted of a dispersion of an aqueous phase into an oil-based phase. The dispersed water-solution phase consisted of 75 vol. % propylene glycol, balance water. The continuous oil phase was made of mineral oil and lanolin. Symphytum components made up 0.004- 0.01 wt. % of the resulting formulation. This emulsion proved to be unstable upon shelf storage at room temperature. After extensive experimentation with processing variables, a stable W/O emulsion was prepared that contained about 0.01 wt. % Symphytum components in the dispersed propylene glycol solution phase and a blend of beeswax, lanolin, and vegetable oil in the continuous oil phase.

SUMMARY OF THE INVENTION

The main object of this invention is the preparation of Concentrated Fluid Symphytum Extracts, defined as CF Symphytum Extracts, prepared for therapeutic use by means of polyphase extraction from *Symphytum* plant matter. For the purpose of this specification and claims, CF Symphytum Extracts are defined as those organic and inorganic constituents which are: (a) present in either fresh or air-dried plant matter, including at least one of the plant elements comprising flowers, seeds, leaves, stems and roots, of any one or more *Symphytum* species including *S. officinale, S. asperum, S. armeniacum, S. tauricum, S. sylvaticum, S. anatolicum, S. icaricum, S. orientale, S. kurdicum, S. pseudobulbosum, S. S. circinale, S. ottomanum, S. icaricum, S.*

brachycalyx, S. aintabicum, S. longisetum, S. bommuelleri, S. tuberosum, S. bulbosum, S. ibericum, or S. longipetiolatum, harvested at a mature stage i.e., peri-bloom, and (b) can be extracted in a controlled or recirculated environment with fluids in either a liquid or vapor state from whole parts or comminuted particles of any or all of the above-named plant elements at temperatures in the range of 20- 80 deg. C with an extractant- fluid contact interval of 1 to 200 hours and with starting input weight ratios of extract fluid/ plant matter of 0.01/1 up to 10000/1. According to this definition, the fluid may be initially a vapor phase which permeates into the plant elements and will under equilibrium conditions and then nucleate and condense a liquid phase on and within the plant elements. Further, according to this invention the fluid may initially contain medical-type surfactants which enhance its capillary flow within the structure of the plant matter. Further according to this definition, the types of defined contact between the plant elements and the extracting fluid include gravity flow of a liquid condensate, gravity drainage of a liquid fluid sprayed from the upper zones of the reactor, circulation/ fluidization by means of vapor phase with or without a dispersed equilibrium aerosol and forced convection circulation/ fluidization by means of a liquid fluid. Still further according to this definition, the defined extraction environment includes inert gases and/ or condensable vapor phases in the range of pressures from 1 to 500 kPa.

Another general object of the present invention is to provide new, improved therapeutic forms and compositions of CF Symphytum Extracts which can be used for dermatological treatment of a number of skin and mucosal membrane conditions in humans and animals. These conditions include but are not limited to: skin dryness/ allergies/ rashes, tissue healing, prevention of scaring complications, fungal infections, treatment of minor burns, etc.

The invention includes various physical forms of the CF Symphytum Extracts (emulsions, liposomes, aerosols) which are not available commercially or reported in the scientific literature. It is believed that the solubility of *Symphytum* extracts is enhanced in the small-diameter-particles relative to typical bulk-solution forms.

The invention includes therapeutic and dermatological formulations in various physical forms with high concentration levels of CF Symphytum Extracts e.g., higher than any known "Comfrey" preparations or published "Comfrey" treatment protocols. Liquid preparations according to this invention contain CF Symphytum Extract components in excess of 0.02 wt.% of the total weight of the final preparation as used. The use of such enriched formulations according to this invention, thus allows smaller quantities of the preparation to be used to deliver the same amount of active components of the *Symphytum* extract.

In emulsion-type formulations, this invention includes topical CF Symphytum Extracts consisting of O/W emulsions, oil being the dispersed phase and water the continuous phase, for the purpose of protecting, moisturizing, and stimulating the healing processes of skin or mucous membrane.

Skin-treatment O/W emulsion formulations according to this invention contain selected oils for moisturizing the skin, especially the *stratum corneum* and high levels of CF Symphytum Extracts in the water phase for maximal healing properties.

This invention also includes improved methods for use of CF Symphytum Extract formulations in alternative physical forms including liquid emulsions such as spray, gel, lotion, cream, ointment, and dispersed vesicles, particles or droplets solid- or liquid-aerosols, liposomes, microemulsions, for maximum effectiveness in wound healing.

This invention includes new methods for controlled-release of CF Symphytum Extracts impregnated into a fibrous matrix or blended with an adhesive.

Patients with AIDS usually experience skin breakdown problems, e.g., folliculitis, "itchy red bumps", psoriasis, and dry itchy skin. Topical emulsion preparations of CF Symphytum Extracts according to this invention significantly relieve the itching in many cases and help promote healthier skin.

Healthcare workers – because of frequent hand washing and wearing surgical gloves – often experience dermatitis, i.e., severe chapping and dryness of the skin. Topical emulsion-type CF Symphytum Extracts formulations according to this invention reduce dryness and, in many cases, stimulate healing to point that the skin becomes healthy again. Similarly, workers who are exposed to irritating substances in their occupation can use similar CF Symphytum extracts formulations for either therapeutic or prophylactic purposes.

Diabetic patients often experience dry skin and in some cases stasis ulcers which heal with difficulty. Topical emulsion-type CF Symphytum Extract formulations according to this invention help relieve the dryness and in some cases has proven to be a good healing agent for the stasis ulcers.

Paraplegics or bedridden patients can experience pressure sores or decubitis ulcers. Topical emulsion-type CF Symphytum Extract formulations according to this invention help condition the skin and thus prevent the formation of the ulcers. Further, the formulations will stimulate the healing of those ulcers already extant.

Other uses for emulsion-type CF Symphytum Extract formulations according to this invention include: diaper rash, chapped or dry skin, sunburn, insect bites, minor wounds, cold sores, athlete's foot, and minor burns.

PREFERRED EMBODIMENTS

One preferred formulation of this invention is an O/W emulsion with at least 0.02 wt.% of active components within CF Symphytum Extracts prepared as described in the following.

CF Symphytum Extract preparation. Preferrably, fresh Symphytum leaves/ stems or roots are used, and at least 12 grams of roots or 60 grams of leaves/ stems are comminuted into one liter of liquid aqueous extracting fluid. Alternatively CF Symphytum Extract is made by comminuting at least 6 grams of dried *Symphytum* leaves and stems or dried roots and combining it with one liter of liquid aqueous extracting fluid. In this context, "dried" denotes less than 10 wt. % water, on an absolute or "bone-dry" basis.

For another preferred embodiment, the extracting fluid may be an undiluted or "neat" liquid such as propylene glycol, glycerol, ethyl alcohol, water, methylene chloride and the chamber environment is the vapor of the liquid at a pressure of about 100 kPa. Alternatively, the extract fluid may be a liquid solution or two-phase emulsion. The extraction process requires approximately 72 hours contact at temperatures between 20 and 30 deg. C. The supernatant extract is filtered thru typical food-type paper filters (nominal pore size 10-100 micrometers).

In the case of extraction with a physiologically- compatible solution (generally isotonic to blood and tissue, 250-350 mOsm/kg), the filtrate may be used directly to prepare final liquid formulations for use in intravenous, subcutaneous, intramuscular, intralymphatic, intraperitoneal, or intraplueral preparations.

Alternatively, the filtrate may be evaporated to reduce the extractant to as little as zero %. To facilitate preparation of certain formulations or physical forms, the extraction step can be done with water or aqueous solutions containing a reduced level of physiologic components (such as saline) and the final adjustment to physiologic osmolality range being accomplished by addition of specific concentrates to the filtered CF Symphytum Extract.

The concentrated filtrate can be added directly to the water phase or it can be re-suspended with an alternative vehicle , e.g. water, glycerol, propylene glycol. One kilogram of the final formulation contains CF Symphytum Extract from at least 6 grams of dried leaves and stems or roots, or the extract from at least 60 grams of fresh leaves/ stems or the extract from at least 12 grams of fresh roots.

In typical O/W emulsions, the volume percent of the dispersed phase is in the range of 0.1- 25 vol. %. For these formulations, the major quantity of CF Symphytum Extract is contained in the water-solution phase of the emulsion, whether it is a simple O/W emulsion or a complex W/O/W emulsion wherein water is the continuous phase and the primary dispersed phase is oil droplets which in turn contain smaller droplets of the continuous phase, water. W/O/W dispersions may also be called double or multiple emulsions.

Liposome dispersions of CF Symphytum Extracts can be made spontaneously by the technique of adding a quantity of aqueous extract solution to a dry film of lipid or phospholipid. Other known alternative methods of forming liposomes such as injection, reverse- micelle formation and reverse-phase evaporation can also be used to produce liposomes from aqueous CF Symphytum Extracts. The therapeutic characteristics of the resulting vesicles can be tailored for specific diseases or tissue applications by: (a) altering the average diameter /size of the vesicle, (b) altering the surface charge of the vesicle, (c) altering the stiffness of the encapsulating vesicle membrane- film and (d) incorporation of antibodies or ligands into the vesicle surface/ film which show binding or affinity for specific types/ forms of tissue.

Aerosol dispersions of solid- or liquid- phase CF Symphytum Extracts can be made by techniques such as atomization, nebulization, spray drying, freeze drying.

EXAMPLES

Group A. Examples of processes for : (a) preparation of the *Symphytum* plant materials to be extracted and (b) the preparation including refining (filtration/ concentration/ purification) of CF Symphytum Extracts.

Example A1. Peri-Harvest Treatment Protocol 1012

This is a process of peri-harvest conditioning/ treatment/ handling of the plant materials i.e., leaves, stems and/ or roots, of *Symphytum* species which preserves their medicinal agents against evaporation, chemical degradation and photochemical inteactions in the time interval between harvest and initiation of the extraction contact including the steps of:

(a) by visual inspection and other chemical/ microbiological tests, selecting zones of the production field which contain *Symphytum* plants which have reached an optimum level of maturity (peri-bloom stage) and are essentially free of disease and have no significant levels of undesirable materials/ bacteria (e.g., pyrrolozidine alkaloids) or adventitious contaminants,

(b) treating selected zones of plants to be harvested with solutions containing for example viable *Lactobacillus planterum* which can reduce the numbers of undesirable adventitious bacteria such as *E. coli or Klebsiella*,

(c) charging the harvested plant materials immediately (within a time period of 10- 50 minutes) into a closed collection apparatus which prevents exposure to sunlight, and

(d) transferring the collected plant materials into specialized extraction apparatus for additional processing.

Example A2. Compression/ Liquid-Fluid Extraction Process for Concentrating *Symphytum* Extracts

This is a method of compacting/ comminuting/ extracting fresh plant materials of *Symphytum* species which includes the steps :

(a) receiving collected plant materials from an enclosed in-field collection/ processing apparatus (see Example A1 above),

(b) comminuting the plant materials to small pieces (avg. length dimension approx. 1 mm) by known processes such as chopping or macerating,

(c) charging the comminuted plant material into an closed reactor within a time interval of 2- 6 hours after receipt,

(d) charging the reactor with a liquid or liquid- mixture extracting fluid such as alcohol or water or propylene glycol or glycerol or mixtures of these components at a selected temperature in the range between 15- 55 deg. C,

(e) contacting the enclosed plant materials under sealed environmental conditions for a time of 2 to 100 hours, preferably 4- 8 at a pressure of 50- 200 kPa, with controlled mechanical agitation by means of blades, or a rotating/ tumbling reactor chamber, and

(f)..treating the extact mixture (fluid and solids) by one or more mechanical separation methods such as sedimentation, centrifugation, filtration, etc., to separate the solid matter. Additional diatomaceous-earth filtration treatment of pre-treated liquid from prior steps may be used to remove color bodies.

Example A3. Preservation Technics For CF Symphytum Extracts

For the case of liquid- fluid aqueous extract solutions (from Example A2 above) which must be stored for extended periods in a bulk tank (to prevent growth of microbes) by either:

(a) adding a small amount (0.001 to 1.0 wt. %) of one or more chemical preservatives such as methyl and propyl paraben, or blends thereof, or

(b) dewatering the active CF Symphytum Extracts to a dry- powder form by vacuum evaporation, spray drying, freeze drying,

Example A4. Air Drying and Storage- Preparation Process for *Symphytum* Plant Elements

This is a process for preparing harvested *Symphytum* plant elements to be stored for extraction at a future time which includes the steps of:

(a) removing water from the plant elements to reduce their water content to 10 wt. % or less, by a flow of heated, dried air (50% RH max, max. air temperature below 65 deg. C, times may range from 10 to 100 hours depending upon the actual RH and flow rate) through a loose bed or across the surface, starting at step (d) of Example A1. above, and

(b) charging the resulting dried plant elements into sealed, radiation- impervious containers along with an inert, air- excluding fluid atmosphere such as volatile alcohol or fluorocarbon which prevents chemical degradation of the active constituents.

Group B. Examples of different topical O/W - emulsion dermatologic formulations which contain CF Symphytum Extracts, e.g., ointment, salve, lotion, cream, spray, infusion fluids, etc. In these examples, the CF Symphytum Extract is dissolved into the indicated quantity of carrier solution or base such as water, glycerol, propylene glycol.

Example B1. Water- Based CF Symphytum Extract Solution

A.	Water Phase	
	CF Symphytum Extracts	2-20 grams
	distilled water	1000 grams
	methyl paraben	1 gram
	propyl paraben	0.5 gram

Example B2. DH100 formulation

A.	Water Phase		% by weight
	methyl paraben	17.0 grams	0.102%
	propyl paraben	8.5 grams	0.051%
	triethanolamine	903. grams	5.433%
	allantoin	152. grams	0.914%
	deionized or distilled water	9375. grams	56.402%
	CF Symphytum ext. in glycerol	2340. grams	14.078%
B.	Oil Phase		
	stearic acid	600. grams	3.611%
	glyceryl monostearate	1575. grams	9.476%
	cetyl alcohol	840. grams	5.054%
	olive oils	320. grams	1.925%
	castor oil	230. grams	1.384%
	jojoba oil	230. grams	1.384%
	myrrh oil	30. grams	0.180%
	peppermint oil	1.25 grams	0.008%
		16,621.75 grams	

C. Heat both phases to 73°C pour A into B while mixing to form a W/O/W emulsion. Continue mixing until the temperature of the mixture is 65°C or less.

Example B3. SCP100 formulation

A.	Water Phase		% by weight
	CF Symphytum Ext. in glycerol, or deionized or distilled water	624. grams	13.675%
		3250. grams	71.225%
	allantoin	50. grams	1.096%

methyl paraben	5. grams	.111%
propyl paraben	2.5 grams	.055%
diazolidinyl urea	10.5 grams	.230%

B. Oil Phase

stearic acid	144. grams	3.156%
cetyl	208. grams	4.558%
olive oil	54. grams	1.183%
castor oil	34. grams	.745%
jojoba oil	34. grams	.745%
myrrh oil	10. grams	.219%
polyoxyethylene (2) stearyl ether	34. grams	.745%
polyoxyethylene 21 stearyl ether	103. grams	2.257%
	4,653. grams	

C. Heat both phases to 73°C. Pour A into B while mixing to form a W/O/W emulsion. Continue mixing until the temperature of the mixture is 50°C or less.

Example B4. DC102 formulation

A. Water Phase

		% by weight
methyl paraben	1. grams	.100%
propyl paraben	0.2 grams	.020%
CF Symphytum Ext. in glycerol	150. grams	14.851%
allantoin	10. grams	.990%
sodium ascorbate	10. grams	.990%
polysorbate 80	10. grams	.990%
deionized water	576. grams	57.030%

B. Oil Phase

stearic acid	40. grams	3.960%
glyceryl monostearate	105. grams	10.396%
steryl alcohol	56. grams	5.544%
liquid petrolatum	52. grams	5.149%
	1,010. grams	

C. Heat both phases to 73°C. While mixing add B into A to form an W/O/W emulsion. Continue mixing until the temperature of the mixture is 50°C or less.

Example B5. DC139 formulation

A.	Water Phase		% by weight
	methyl paraben	20. grams	.100%
	propyl paraben	4. grams	.020%
	CF Symphytum Ext.in propylene glycol	2953.grams	14.794%
	allantoin	204. grams	1.022%
	polysorbate 80	200. grams	1.002%
	deionized or distilled water	11,520. grams	57.713%
B.	Oil Phase		
	stearic acid	800. grams	4.008%
	glyceryl monostearate	2100. grams	10.521%
	steryl alcohol	1120. grams	5.611%
	liquid petrolatum	1040. grams	5.210%
		19,961. grams	

C. Heat both phases to 73°C. Pour B into A while mixing to form an O/W emulsion. Continue mixing until the temperature of the mixture is 50°C or less.

Example B6. SCP293 formulation

A.	Water Phase		% by weight
	methyl paraben	20. grams	.097%
	propyl paraben	12. grams	.058%
	CF Symphytum Ext. in glycerol	3084. grams	14.980%
	allantoin	202. grams	.980%
	triethanolamine	400. grams	1.900%
	distilled water	15,000. grams	72.880%
B.	Oil Phase		
	stearic acid	268. grams	1.300%
	glyceryl monostearate	700. grams	3.400%
	cetyl alcohol	374. grams	1.820%
	olive oil	214. grams	1.040%

castor oil	168. grams	.820%
jojoba oil	100. grams	.490%
myrrh oil	40. grams	.190%
peppermint oil	1.25 grams	.006%

C. Heat both phases to 73° deg. C Pour A into B while agitating to form a water-in-O/W emulsion. Continue mixing until the temperature of the mixture drops below 50°C.

From 0.5- 5.0 wt. % of *Melaleuca uncinata* oil (frequently called Tea Tree oil) can be added to any of the examples (B1 to B6 above) for the purpose of inhibition of fungal growth at a dermal application site e.g., athlete's foot treatment, applied between toes.

Group C. Examples of non- emulsion CF Symphytum Extract pharmaceutical formulations i.e., single-phase solutions, vesicles, liposome, micelles, aerosols, tablets, microcapsules, caplets, injectable fluids, transdermal delivery patch/ device, etc.

Example C1. Isotonic Liposome Formulation LS141

Isotonic liposomes are desirable for application of CF Symphytum Extracts to sensitive tissue, wounds, mucous membrane, or as an ingredient in an injectable, implantable, or inhalable preparation.

Use water phase from example B1 above; adjust the solution osmolality to physiologic range (250- 350 mOsm/kg) by the addition of concentrates containing physiologic salts, glucose, etc.. Form the liposome by adding the solution to a dry film of lipid such as lecithin or cholesterol; use sonication if needed.

Example C2. Aerosol Formulations A293

Aerosol formulations are of particular value in application of CF Symphytum Extracts to hairy areas of human or animal bodies.

In order to prepare lyophilized solid forms of CF Symphytum Extract, the extraction stage would be done with a minimal amount of water or alcohol to facilitate dewatering by evaporation, spray drying or freeze drying. Solid aerosols can be used with pressurized propellants in devices which meter and disperse the dry particles into a gas-type aerosol which may be inhaled for treatment of nasal membranes.

For liquid dispersions, a known vesicle- or emulsion- stabilizing agent is dissolved into a volatile, biocompatible propellant- solvent such as R-12 fluorocarbon. The resulting fluid is packaged into a pressurized propellant spray device to facilitate direct external application to scalp, skin or mucosal tissue.

Example C3. Transdermal/ Transmucosal formulation A291

CF Symphytum Extracts such as Example B1 above are blended with known skin adhesive compounds to produce a diffusion- controlled drug delivery reservoir. Additional selected therapeutic agents may also be added for specific functions such as: (a) low levels of DMSO for enhancing the rate of absorption of the *Symphytum* healing agents into the skin, or (b) or synergistically increasing the healing properties of the CF Symphytum Extracts e.g., D-alpha-tocopherol in transmucosal adhesive devices.

Example C4. Microencapsulated formulations M 17-19

Dry- powder forms of CF Symphytum Extracts such as Example B1 dewatered by the process of Example A3(b), are encapsulated as microspheres (0.01 to 1.0 mm diam.) within thin, polymeric membranes using known spray- drying technics. These forms can be used for controlled release in transdermal, transmucosal, enteral, or paraenteral preparations.

D. Examples of selected methods of using various formulations of CF Symphytum Extracts (see Groups A., B. and C. above).

Example D1. Adhesive patch for delivering controlled amounts/ rates (skin, mucous membrane). Aqueous emulsion CF Symphytum Extracts is added during the preparation of a known hydrogel adhesive for use on human skin so that the resulting cast layer or film serves as a reservoir matrix and a diffusion- controlled delivery means for the active agents of the extract.

Example D2. Conductive electrode adhesive formulations with CF Symphytum Extract (TENS, long-term EKG monitoring, iontophoresis, etc.).

One frequent complication of transdermal electrostimulation for the relief of pain is a skin rash which develops in the tissue layers subject to the effects of the material, current pulses and the conductive electrode gels/ creams. Similarly, electrocardiac monitoring apparatus, such as a Holter monitor, and iontophoresis devices also can produce painful skin rashes. CF Symphytum Extracts are blended into the conductive paste or the skin adhesive to alleviate these conditions (see Example D1 above).

Example D3. Impregnated tampon for delivering selected CF Symphytum Extract dosage to intravaginal membranes. An emulsion formulation such as Example B2 with Tea-Tree oil addition is used. Alternatively, a liposomal formulation such as Example C1 is used; by the addition of a binding ligand or antibody specific for the critical fungal vector e.g., candida albicans, to the vesicle surface, the vesicles is targeted directly toward the infectious process.

Example D4. Microencapsulated or dry- powder aerosol forms of CF Symphytum Extracts such as Example C2. is administered by known metering aerosol devices for the treatment of throat or nasal irritations/

inflamations which may occur in accident situations involving poison-gas attacks, fires, explosions, and exposures to irritating chemical vapors/ mists.

Example D5. Liquid aerosol or liposome forms of CF Symphytum Extracts is administered by a spray dispenser for scalp treatment e.g., sunburn or hair-loss. For enhanced hair-growth stimulation, CF Symphytum Extracts are blended into known compounds. Similarly, for the treatment of aging and skin wrinkles, CF Symphytum Extracts are blended with compounds which are known to improve the elastic tone and thickness of the skin layer structure; for such conditions, a known acoustic or ultrasonic device is used used along with the application to accelerate absorption into the skin.

Example D6. Wax-type suppository for colitis treat. CF Symphytum Extracts are blended into a known suppository vehicle prior to forming the suppository device.

Example D7. CF Symphytum Extracts for Treating Skin Conditions Related to HIV Virus
Study 2303- 10 patients, formulation of Example B2 used for about 6 months for eczema, folliculitis, and dry itchy skin.
RESULTS: About half the patients indicated symptomatic relief and requested additional supplies of the formulation for continuing use.

Example D8. CF Symphytum Extracts for Treating Skin Lesions Related to Kaposi's Sarcoma (KS) in HIV Population
Study 1011- Small-group test of formulation of Example B2. Used for KS skin wounds/ eruptions.
RESULTS: Formulation cleared up most skin problems and closed spots.

Example D9. CF Symphytum Extracts for Skin Problems In Diabetes Population
Study 805. Group of 98 diabetes patients used formulation in Example B6 over a period of about 30 days for treatment of dry skin and other diabetes-related skin complications. Written evaluation instrument given to each participant to mail in at the completion of the test period. For the preliminary report, the data on 39 questionaire responses was analyzed.
RESULTS: About 87% of the respondents indicated that the formulation was satisfactory or very satisfactory for the relief of dry-skin complications.

CLAIMS

The preceeding examples of this invention can be repeated with similar success by susbstituting the generically or specifically described reagents for those used in the examples.

From the examples presented and previous descriptions, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various starting materials, body-healing usages and administration forms/ conditions.

I claim:

1. A therapeutic composition for treating minor sunburn, rashes, abrasions, wounds, and itching conditions of the skin or moucous membranes of mammals consisting of: (a) 3-75 wt. % CF Symphytum Extracts and (b) pharmaceutical vehicle = balance.

2. The therapeutic composition of Claim 1 wherein the composition is in the physical form of a stablized, oil-in-water emulsion having at least 10 wt. % CF Symphytum Extract dissolved in the continuous aqueous phase.

3. The therapeutic composition Claim 2. wherein the said oil-in-water emulsion contains therapeutic amounts of additives including one of more of: vitamins, hormones, peptides, preservatives, skin moisturizers, essential oils, waxes, or soaps.

4. The therapeutic composition of Claim 1 wherein the composition is in the form of a liposome having at least 10 wt. % CF Symphytum Extract dissolved in the continuous aqueous phase and at least 10 wt. % CF Symphytum Extract in the vesicle-encapsulated solution.

5. The therapeutic composition of Claim 4 wherein the said vesicle- encapsulated solution and the said continuous phase contain therapeutic additives including one or more of: vitamins, hormones, peptides, preservatives, skin moisturizers, or essential oils.

6. The therapeutic composition of Claim 1 wherein the composition is dispersed into fine particles or droplets in the form of an liquid or solid aerosol.

7. A method of preparation of CF Symphytum Extracts which comprises the steps of:
(a) charging a unit quantity of plant matter from one or more mature *Symphytum* species into a closed extraction chamber capable of supporting an absolute internal pressure in the range 10- 500 kPa,

plant matter in the range 0.01 up to 10000 and which further has a defined composition, mass ratio of liquid to vapor phase, temperature, pressure and flow velocity into the said extraction chamber, and

(c) contacting the said plant matter and the said extraction fluid under a set of staged, controlled cycles of time, temperature, pressure, reflux, and convection within the said extraction chamber sufficient for extraction of CF Symphytum Extracts.

8. The method of Claim 7. wherein the fluid is a quantity of liquid solution which amounts 100- 1000 times the mass of the said plant matter which is injected at a temperature of 50-70 deg. C at a pressure of 90- 110 kPa as a refluxed spray with a average velocity of 0.5- 3 meter/ sec over a period of time sufficient for extraction of CF Symphytum Extracts.

9. The method of of Claim 8. wherein the fluid is a liquid water solution containing up to 0.01 wt. % of a known pharmaceutical surfactant and the contact period consists of a single cycle of 100-200 hours duration at 50- 70 deg. C, 90- 110 kPa, and a forced convection velocity of 0.1- 3 meter/ sec.

10. The method of Claim 7. wherein the said set of contacting cycles consists of a first sub-atmospheric pressure cycle of 1-20 hours duration at 30- 90 kPa, 50- 70 deg. C, and a forced convection velocity of 1- 5 meter/ sec followed by a second higher-pressure cycle of 180- 200 hours duration at 100- 200 kPa, 40- 60 deg. C, and a forced convection velocity of 0.5- 5 meter/ sec.

11. A method of treating skin wounds, irritations, rashes or abrasions of humans or animals to enhance the healing processes comprising administering a wound-healing amount of CF Symphytum Extract.

12. The method of Claim 11. wherein the CF Symphytum Extract is in the form of a O/W emulsion which is applied directly to the area to be treated by pouring, spraying, daubing, spreading or rubbing.

13. The method of Claim 11. wherein the CF Symphytum Extract is administered in a fine-disperse form such as a liposome or aerosol to the area to be treated.

14. The method of Claim 11. wherein the CF Symphytum Extract is dispersed within an adhesive matrix which is applied directly to the skin or mucosal area to be treated.

15. A method of treating fungal infections of the skin or mucosa by the administration of a fungicidally effective amount of a CF Symphytum Extract.

16. The method of Claim 15. wherein the CF Symphytum Extract is in the form of an O/W emulsion which is applied directly to the skin or mucosal area to be treated by pouring, spraying, daubing, spreading or rubbing.

17. The method of Claim 15. wherein the CF Symphytum Extract is impregnated into a fibrous, dispensing matrix which is held in light mechanical contact with the skin or mucosal area to be treated.

18. A method of preventing skin rashes associated with long- duration skin electrodes by administration of a contact-rash-preventive amount of CF Symphytum Extract to the skin area subject to irritation due to contact with the electrode material or related current- flow patterns.

19. The method of Claim 18. wherein the CF Symphytum Extract is blended with the electrode adhesive or electrode contact paste in defined zones of the skin- contact area including a peripheral strip amounting to 10- 30% of the electrode area.

20. The method of Claim 18. wherein the CF Symphytum Extract is in the form of a permeable, controlled-release polymer foam matrix which is attached to defined contact zones of the electrode known to produce skin irritation.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/07747

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5): A61K 35/78
U.S. CL: 424/195.1

II FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	424/45, 195.1, 401, 405, 450, 486

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	US, A, 4,670,263 (NOORLANDER) 02 JUNE 1987; See entire document.	1-20

[10] Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
30 December 1991	19 FEB 1992
International Searching Authority	Signature of Authorized Officer
ISA/US	Carlos Azpuru

Form PCT/ISA/210 (second sheet) (Rev.11-87)